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Antimicrobial resistance in zoonotic enteric pathogens

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Summary

Antimicrobial resistance is a zoonotic health threat. As in humans, the use of antimicrobial agents in animals results in the emergence and spread of resistant bacteria. Resistant bacteria from animals may be passed to humans via the food chain or direct animal contact, and may result in resistant infections. Increasing prevalence of resistance to antimicrobial agents such as fluoroquinolones and third-generation cephalosporins, which are important for the treatment of infections caused by enteric pathogens, has significant public health implications. Controlling the spread of resistance requires the collaboration of several partners, including the farming, veterinary, medical, and public health communities.

Keywords

Agriculture – Antimicrobial – Campylobacter – Fluoroquinolone – Food animal – Foodborne – Resistance – Salmonella.

Introduction

Antimicrobial resistance is a daunting public health threat impacting both human and animal health and it is a cause for concern wherever antimicrobial agents are in use (in hospitals, in the community, on farms, etc.). The use of antimicrobial agents in food animals results in antimicrobial resistance among pathogenic and commensal bacteria in these animals, and the resistant bacteria (or the resistant genetic determinants) may then be transmitted to humans through the food supply or by direct contact with animals (14). The most common way that humans become infected with zoonotic enteric pathogens is through the ingestion of foods contaminated with animal faeces (contamination usually occurs during processing).

Antimicrobial resistance is emerging and spreading among some foodborne bacteria. *Campylobacter* and *Salmonella* are two examples of foodborne pathogens in which increasing resistance, particularly to fluoroquinolones and third generation cephalosporins, is a concern. Multi-drug resistance is also a worrying possibility, particularly among *Salmonella*. Multi-drug resistant *S.* Typhimurium definitive type 104 (DT104) (26) and multi-drug resistant *S.* Newport (11) have both caused recent foodborne outbreaks. Pathogenic bacteria are not the only concern when considering antimicrobial resistance in bacteria with food animal reservoirs. Commensal bacteria are a less obvious threat, but can also be transferred from animals to humans through the food supply or through direct contact. These bacteria may carry transferable genetic determinants of resistance and serve as a reservoir of resistance genes for pathogenic bacteria (41, 71).

Antimicrobial agents have been used in agriculture since the early 1950s to treat infections and improve growth and feed efficiency. The precise number of antimicrobial agents used in agriculture is not known, however, a substantial portion of the total amount are given to food animals for growth promotion. Antibiotics used for growth promotion, a practice that is coming under increasing scrutiny (46), are generally given in sub-therapeutic doses and in the

absence of disease. The World Health Organization (WHO), following consultations in 1997 and 1999, has recommended that the use of antimicrobial growth promoters that belong to classes of antimicrobial agents used in humans be discontinued (80, 82). The same recommendation was made by the Institute of Medicine in the United States of America (USA) in 2003 (34).

Several European countries have taken steps toward this goal. Due to consumer concerns about antimicrobial resistance, farmers in Denmark voluntarily stopped using antimicrobial agents as growth promoters in 1999 (1). This voluntary action has reduced the annual total volume of antimicrobial agents used in food animals in Denmark by 60% (from 206 metric tons [MT] in 1996 to 81 MT in 2001) (17, 65). In 2001, the European Union (EU) banned farmers from using antimicrobial agents related to human medicine for growth promotion (19). Drugs which were banned include avoparcin, tylosin, spiramycin, bacitracin, and virginiamycin (19). The Health Ministries in the EU have also recently agreed to discontinue the use of all remaining antimicrobial growth promoters (20).

In Denmark, studies performed in the broiler chicken industry to investigate the result of their action to remove antimicrobial growth promoters have shown no negative consequence for farm profits or animal health (84). Similar conclusions were reported in fattening pigs, although an increase in diarrhoea in weaned piglets required other interventions, such as a change in feeding and weaning procedures (84). In Sweden, all use of antimicrobial agents as growth promoters was banned in 1986, decreasing their total usage by 55%, without long-term adverse affects on productivity. This demonstrates that it is possible to achieve competitive production results in the absence of antimicrobial growth promoters (27, 76). The discontinuation of antimicrobial growth promoters in these countries has been followed by a decrease in antimicrobial-resistant bacteria in animals, food products, and humans (1, 6, 17, 38, 56, 73).

The agricultural use of antimicrobial agents related to those used in human medicine increases the likelihood that human bacterial pathogens with food animal reservoirs will develop resistance or cross-resistance to drugs approved for use in humans (62). In the USA, antimicrobial resistance is increasing in the foodborne pathogens *Salmonella* and *Campylobacter* (12). This limits the choice of therapeutic agents and increases the potential for treatment failures and adverse clinical outcomes (69). In addition, patients who are taking antimicrobial agents for any reason are at increased risk of acquiring antimicrobial-resistant foodborne infections (7, 8). If antimicrobial agents are to be effective in humans and food animals they must be used appropriately. While therapeutic use of antimicrobial agents in food animals is important for animal health, the long-term effectiveness of antimicrobial agents used in human medicine must be preserved. This report presents information on the frequency of resistant foodborne infections in the USA, reviews scientific evidence linking antimicrobial agent usage in agriculture to resistant foodborne infections in humans, and makes recommendations for measures to protect public health.

Antimicrobial use in food animals

At least seventeen classes of antimicrobial agents are approved for growth promotion (also called improved feed efficiency) in the USA. These include tetracyclines, penicillins, macrolides, lincomycin (an analog of clindamycin) and virginiamycin (an analog of quinupristin/dalfopristin). To understand the human health consequences of the agricultural use of antimicrobial agents, evaluating the quantity of antimicrobial agents and how they are used in food animals in the USA is important. This issue was recently highlighted in a report by the General Accounting Office (25). Unfortunately, no public health reporting system exists for the quantity of antimicrobial agents used in food animals in the USA. The Animal Health Institute, which represents 80% of the companies that produce antimicrobial agents for animals in the USA, estimated that their member companies produced 8,200 MT of antimicrobial agents for use in food animals in the USA in 1998 (5). An alternative estimate was provided by the Union of Concerned Scientists (UCS) in 2001, which calculated that 14,000 MT of antimicrobial agents are used annually in food animals in the USA (46). According to UCS estimates, 93% (12,700 MT) of the antimicrobials used in agriculture are used in the absence of disease (46). The UCS also estimates that less than 1,400 MT of antimicrobial agents are used annually in humans in the USA (46). Though more precise data on the quantity and purpose (e.g. therapeutic versus growth promotion) of antimicrobial agents used in food animals are needed, these initial estimates provide some perspective on the large quantity of antimicrobial agents used in food animals in the USA.

The selective pressure exerted by the use of antimicrobial agents in food animals promotes the emergence and dissemination of antimicrobial-resistant bacteria: animal pathogens, human pathogens with food animal reservoirs, and commensal bacteria (14, 31, 32). These resistant bacteria may be transferred to humans either through the food supply or by direct contact with animals (37, 55, 79).

Commensal bacteria

If commensal bacteria, which are naturally occurring in the host, are exposed to antimicrobial agents, they may become resistant and be able to transfer resistance genes to pathogenic bacteria. Antimicrobial resistance in the commensal bacteria of humans and animals results largely from the selective pressure of antimicrobial agent use and reflects the genetic elements that may transfer to pathogens (33, 40, 49, 72).

Most resistant bacteria have mobile genetic elements such as R-plasmids and transposons that carry resistance genes. As the number of resistant commensal bacteria increases, the plasmid population becomes larger and may allow more frequent transfer of resistance to pathogenic bacteria such as *Salmonella* and *Shigella*. *Escherichia coli*, which is the predominant species in the normal aerobic faecal flora in humans and many animals, has demonstrated its ability to transfer genes coding for resistance to other species, including pathogenic bacteria (9, 13, 33, 52, 63, 68, 78). Recent studies have shown an emerging resistance in *E. coli* to third-generation cephalosporins. Winokur *et al.*, found 59 (16%) of 377 clinical *E. coli* isolates from cattle and swine and six (1%) of over 1,000 clinical human *E. coli* isolates collected in Iowa to be resistant to extended spectrum cephalosporins. The study identified identical CMY-2 genes, associated with multi-drug resistance and extended spectrum cephalosporin resistance, in resistant isolates from both humans and animals, suggesting that the gene coding for antimicrobial resistance was transferred between animals and humans (78).

Another example of potential animal-to-human transfer of resistant commensal bacteria is quinupristin/dalfopristin-resistant *Enterococcus faecium*. Quinupristin/dalfopristin was approved for use in humans in the USA in 1999 for treatment of vancomycin-resistant *E. faecium* infections. However, virginiamycin, an analog of quinupristin/dalfopristin, has been used as a growth promoter in food animals in the USA since 1974 (15, 58). A study conducted in 1998-1999, before the approval of quinupristin/dalfopristin use in humans, found quinupristin/dalfopristin-resistant *E. faecium* on 58% of chickens purchased in grocery stores from four different states (45). Additionally, quinupristin/dalfopristin-resistant *E. faecium* was found in 1% of the stools from non-hospitalised persons who submitted a stool specimen to clinical laboratories. These findings suggest that virginiamycin use in chickens has created a large reservoir of quinupristin/dalfopristin-resistant *E. faecium* to which humans are commonly exposed. The use of quinupristin/dalfopristin in humans for the treatment of vancomycin-resistant *E. faecium* and other serious infections may contribute additional selective pressure. Similar data in Europe led the EU to ban the subtherapeutic use of virginiamycin in food animals in 1998 (75).

Pathogenic bacteria

The transfer of resistant bacteria from food-producing animals to humans is most evident in human bacterial pathogens which have food animal sources, such as *Campylobacter*, which has reservoirs in chickens and turkeys (2, 67, 70), and *Salmonella*, which has important reservoirs in cattle, chickens, pigs, and turkeys (4, 47). Many countries have established national surveillance programmes to monitor antimicrobial resistance in foodborne enteric pathogens. In the USA, the National Antimicrobial Resistance Monitoring System (NARMS) for enteric bacteria was launched in 1996. The NARMS is a collaboration of several agencies including the Centers for Disease Control and Prevention, the USA Food and Drug Administration (FDA) – Center for Veterinary Medicine, several local health departments, and the health departments of all fifty states. In addition to NARMS, the Foodborne Diseases Active Surveillance Network (FoodNet) conducts population-based studies to estimate the burden and sources of specific foodborne diseases in ten states.

Campylobacter

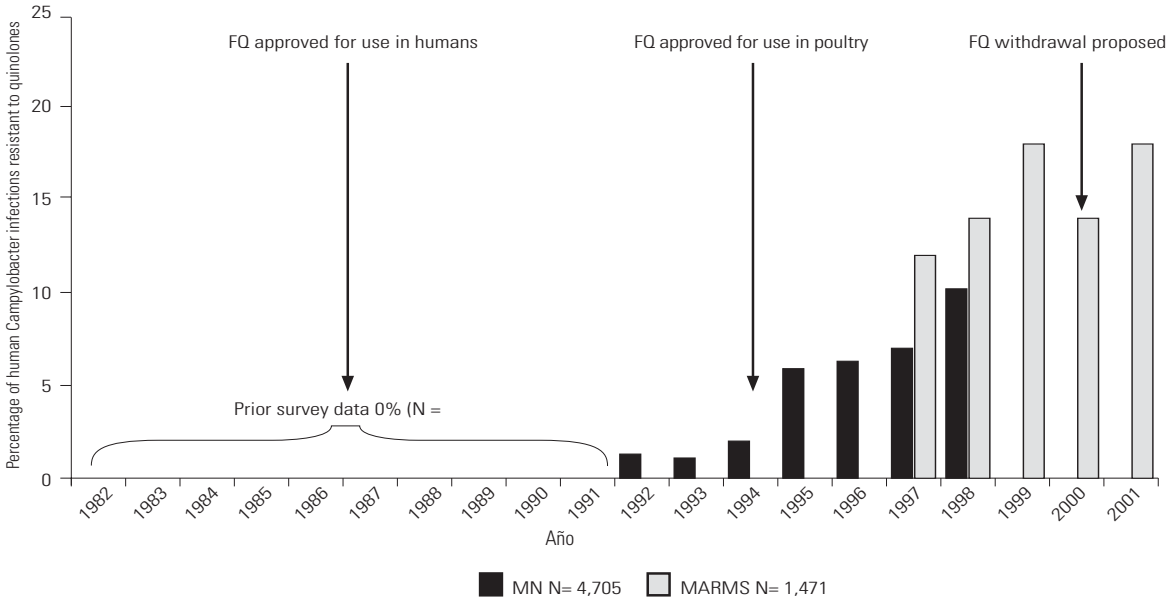
Since 1997, NARMS has monitored the prevalence of antimicrobial resistance among *C. jejuni*, the most common *Campylobacter* in the USA, and C. coli isolated from humans. In 1997, isolates from five sites were examined in the laboratory and twenty-eight (13%) of 217 *C. jejuni* and C. coli isolates were found to be resistant to ciprofloxacin, a fluoroquinolone (12). In 2001, surveillance expanded to nine sites and 75 (19%) of 384 *C. jejuni/coli* isolates proved to be resistant (12). This increase in the prevalence of ciprofloxacin resistance is statistically significant (95% confidence interval: 1.4, 4.1) (12). Between 1997 and 2001, resistance to tetracycline decreased from 47% to 41% and resistance to erythromycin remained at 2% among *C. jejuni/coli* (12). Interviews with patients with ciprofloxacin-resistant *Campylobacter* infections in 1998 and 1999 showed that most patients with ciprofloxacin-resistant infections had not travelled outside the USA before their illness began (36), indicating that the infections were domestically acquired.

The emergence of fluoroquinolone resistance among domestically acquired *C. jejuni* and *C. coli* infections is an

example of antimicrobial resistance resulting from the use of antimicrobial agents in food animals in the USA and the subsequent transfer via the food supply of resistant bacteria to humans. Figure 1 uses data adapted from a study in Minnesota and from NARMS surveillance statistics to depict the timeline of emergence of quinolone resistance in human *Campylobacter* infections (29). Fluoroquinolones (e.g. ciprofloxacin) were approved for human medicine in 1986. A national survey of reported *C. jejuni* and *C. coli* cases conducted in sentinel counties between 1989 and 1990 found no *C. jejuni* or *C. coli* isolates from humans to be resistant to fluoroquinolones (12, 29). The NARMS surveillance data showed that the prevalence of fluoroquinolone resistant *Campylobacter* had risen to 13% in 1997 and 19% in 2001 (12, 29). The first fluoroquinolones approved for use in food animals in the USA were sarafloxacin in 1995 and enrofloxacin in 1996. These fluoroquinolones were approved for the treatment of respiratory disease in chickens and turkeys. Experiments have demonstrated that ciprofloxacin resistance in *C. jejuni* evolves rapidly in chickens treated with these drugs (43).

Campylobacter that are resistant to fluoroquinolones are often also resistant to an elemental quinolone, nalidixic acid. The study conducted in Minnesota reported that *C. jejuni* isolated from humans that were found to be resistant to nalidixic acid increased from 1% in 1992 to 10% in 1998. Many of the early resistant cases were associated with foreign travel (64), correlating to the use of fluoroquinolones in agriculture in other countries before it was used in the USA (81). Nalidixic acid-resistant *Campylobacter* infections that were domestically acquired increased significantly between 1996 and 1998 in Minnesota, a finding associated with the licensure of fluoroquinolones for use in poultry in the USA in 1995 (64). A comparison of molecular subtypes of isolates from humans and domestic chicken products from retail stores in Minnesota showed a similarity between resistant *C. jejuni* strains from chickens and infections diagnosed in Minnesota residents (64). These data suggest that resistant infections in humans are acquired through the domestic food supply as well as from abroad.

In a case-control study of ciprofloxacin-resistant *Campylobacter* infections conducted in the FoodNet sites in 1998 and 1999, domestically acquired ciprofloxacin-resistant *Campylobacter* cases were compared with healthy controls (36). Persons with ciprofloxacin-resistant *Campylobacter* infections were more likely to have eaten poultry cooked at a commercial establishment than were controls (36). Because chicken is not imported into the USA, this finding supports the hypothesis that poultry is an important source of domestically acquired ciprofloxacin-resistant *Campylobacter*. A risk assessment conducted by FDA concluded that the use of fluoroquinolones in chickens in the USA has compromised the treatment with fluoroquinolones of almost 10,000 people a year. This means that each year, thousands of people with *Campylobacter* infections who seek medical care are given fluoroquinolones for infections which are,



FQ: fluoroquinolones
MN: statistics from a study undertaken in Minnesota, 1992-1998
NARMS: statistics from the National Antimicrobial Resistance Monitoring System

Fig. 1
Quinolone- and fluoroquinolone-resistant *Campylobacter* jejuni in the United States of America, 1982-2001 (29)

unbeknownst to the health care worker, resistant to that class of antimicrobials (23). Based on the risk assessment and other evidence that use of fluoroquinolones in poultry has adverse human health consequences, the FDA proposed to withdraw approval of enrofloxacin for poultry in October 2000 (24). The administrative hearings on the FDA proposal – requested by the manufacturer of enrofloxacin for poultry – resulted in a decision by the administrative law judge to uphold the FDA proposal (24). The judge concluded that there was sufficient evidence provided by the FDA to show that use of enrofloxacin in poultry had resulted in fluoroquinolone resistant *Campylobacter*, and that the resistance has been transmitted to humans with significant health consequences. The FDA Commissioner has yet to take a final decision.

Salmonella

The NARMS has also been used to monitor the prevalence of antimicrobial resistance among non-Typhi *Salmonella* since 1996. In 1996, isolates from humans in 14 sites underwent laboratory examination, and 164 (11%) of 1,527 *Salmonella* isolates were resistant to \$5 of the 14 antimicrobial agents tested (12). As of 2001, surveillance had expanded to 17 sites and 336 (15%) of 2,237 *Salmonella* isolates were resistant to \$5 antimicrobial agents (12). In that same time period, resistance to ampicillin increased from 18% to 25% and trimethoprim-sulfamethoxazole resistance increased from 3% to 10% (12).

Third-generation cephalosporins, such as ceftriaxone, are commonly used for the treatment of invasive *Salmonella* infections in children because of their pharmacodynamic properties and low prevalence of resistance to these agents. Since fluoroquinolones are generally contraindicated in children, treatment options in children are limited and the potential emergence of ceftriaxone-resistant *Salmonella* is of concern. The first reported case of domestically-acquired ceftriaxone-resistant *Salmonella* in the USA was in a twelve-year-old child in Nebraska (21). Before the child became ill, the father, a veterinarian, treated several cattle herds for illnesses due to culture-confirmed *Salmonella* infection. No information was available regarding which antimicrobial agents were used in the cattle. However, ceftriaxone-resistant and ceftriaxone-susceptible *Salmonella* serotype Typhimurium variant Copenhagen were isolated from the treated cattle. This is the same serotype isolated from the child. Ceftriaxone-resistant isolates from the child and one of the cows had similar pulse field gel electrophoresis or 'molecular fingerprint' patterns; the isolate from the child had two additional bands. The additional bands were subsequently determined to be from another plasmid, indicating that the *Salmonella* strains were apparently identical. It is likely that use of ceftiofur, a third-generation cephalosporin that is used in cattle and is related to ceftriaxone, contributed to the emergence of ceftriaxone resistance in this strain of *Salmonella* in cattle, which was subsequently transmitted to the child.

The ceftriaxone-resistant infection in the child in Nebraska was not an isolated event (18, 28). In 2001 the NARMS annual report recorded that the percentage of non-Typhi *Salmonella* isolates resistant to ceftriaxone increased from 0.1% in 1996 to 1.5% in 2001 (12). When patients from whom isolates were received in 1996-1998 were interviewed, few reported international travel, suggesting that most infections were domestically acquired (21). Furthermore, ceftriaxone resistance in most domestically acquired infections is due to an AmpC-type resistance gene (bla_{CMY-2}), which resides on a plasmid. The discovery of a similar molecular mechanism of resistance among different *Salmonella* strains suggests that horizontal dissemination of a resistance determinant from one bacterial strain to another may be occurring (18). A 1999 study at the University of Iowa found multidrug-resistant, cephalosporin-resistant bovine, porcine and human *Salmonella* spp. isolates from the same geographical region. All human and animal resistant isolates encoded a CMY-2 AmpC-like protein (77).

The emergence of multidrug-resistant *Salmonella* serotype Typhimurium DT104 in the USA and other countries is an example of how a highly resistant clone of *Salmonella* has the ability to spread among animals and then to humans. Described in 1998 by Glynn *et al.*, the emergence of *S.* Typhimurium DT104 in the USA can be traced back to as early as 1985 (26). Although national surveillance data are lacking, available information indicates that *S.* Typhimurium DT104 ACSSuT spread among animals and then humans in the early 1990s (59). The prevalence of *S.* Typhimurium isolates with the ACSSuT pattern of resistance increased among human *S.* Typhimurium isolates collected in periodic surveys from 0.6% in 1979-1980 to 34% in 1996 (26). Among human *S.* Typhimurium isolates submitted to NARMS, the prevalence of the ACSSuT resistance pattern was 28% in both 1999 and 2000 and 30% in 2001 (12).

Another multidrug-resistant *Salmonella* that is becoming increasingly common is a strain of *S.* Newport. This emerging strain is resistant to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazle, tetracycline, amoxicillin/clavulanate, cephalothin, cefoxitin and ceftiofur, it possesses a decreased susceptibility to ceftriaxone (minimum inhibitory concentration [MIC] > 16 μg/ml), and is designated as multi-drug resistant (MDR) *S.* Newport Amp-C (28). The strain combines the broad resistance spectrum seen in DT104 with an Amp-C determinant similar to that identified in the Nebraska Child in 1998. According to the

2001 NARMS Annual Report (12) *S.* Newport was the third most common serotype of *Salmonella*, making up 9% of all *Salmonella* isolates received. Of these, a remarkable 25% were MDR *S.* Newport (12). Field investigations have demonstrated an association between human MDR *S.* Newport Amp-C infections and eating ground beef (11), drinking and eating unpasteurised dairy products, (42) and living on a dairy farm (28), suggesting that cattle are an important reservoir for MDR *S.* Newport.

In addition to fluoroquinolone-resistant *Campylobacter*, there is also the potential for an emergence of domestically acquired fluoroquinolone-resistant *Salmonella*. There is already evidence of decreased susceptibility to fluoroquinolones, but it is unclear whether this is a result of the selective pressure of agricultural use or of human use of fluoroquinolones. Fluoroquinolones are the most commonly used antimicrobial for the treatment of invasive *Salmonella* infections in adults (4). In 1996, <1% of non-Typhi *Salmonella* isolates collected by NARMS had a decreased susceptibility to ciprofloxacin (MIC > 0.25 mg/ml). In 2001, 3% of isolates had decreased susceptibility to ciprofloxacin (12). The growing percentage of isolates with decreased susceptibility to ciprofloxacin among *Salmonella* infections is of immediate concern because isolates with a MIC > 0.25 mg/ml typically only require a single additional point mutation to become resistant (MIC > 4 μg/ml). Therefore, if the isolates with decreased susceptibility are exposed to continued selective pressure, they may develop resistance (50). Furthermore, patients infected with *Salmonella* strains with a decreased susceptibility to fluoroquinolones may respond poorly to future treatment with that class of antimicrobials (4, 48). For these and other reasons, authors have suggested lowering the clinical breakpoint for determining that an infection is resistant to this antimicrobial agent (16).

There are currently only a limited number of fluoroquinolone resistant *Salmonella*, and those that do exist appear to be related to foreign travel, more specifically, to persons hospitalised overseas, who then introduce fluoroquinolone-resistant *Salmonella* into hospitals and nursing homes when they return to the USA (54). Thus, the limited number of fluoroquinolone-resistant *Salmonella* infections isolated in 2001 may have emerged in nosocomial settings, rather than agricultural ones.

Clinical implications

The clinical implications of growing antimicrobial resistance among zoonotic enteric pathogens include increased enteric illness and more treatment failures. Increased severity of infections and higher mortality have also been associated with antimicrobial resistance in *Campylobacter* and *Salmonella* infections (51, 64, 74, 85).

Increasing numbers of human infections of antimicrobial resistant foodborne pathogens occur due to an interaction between antimicrobial resistant *Salmonella* that are ingested, the native host flora, and antimicrobial treatment. Treatment for any reason may suppress normal protective flora, giving a temporary advantage to resistant bacteria if they are present. For example, taking an antimicrobial agent may lower the infectious dose of *Salmonella* that are already resistant to that antimicrobial agent (7, 8). Bohnhoff *et al.* showed in the early 1960s that the infectious dose of *Salmonella* in mice with an 'undisturbed' normal intestinal flora is about 106 organisms (10). When the normal flora were disturbed by administering streptomycin, the infectious dose for streptomycin-resistant *Salmonella* decreased to only ten organisms. Analyses of antimicrobial resistant *Salmonella* outbreaks have demonstrated that concurrent exposure to antimicrobial agents can result in a larger number of cases than would have occurred if the outbreak had been caused by a sensitive strain (14). Studies of *Salmonella* outbreaks have shown that antimicrobial treatment in humans that precedes and is unrelated to the *Salmonella* infection can predispose humans to infection with either resistant (31, 61, 66) or susceptible *Salmonella* (57). In contrast to the outbreak studies, in cases of sporadic salmonellosis, previous treatment with an antimicrobial agent was a higher risk factor for contracting an antimicrobial-resistant infection (39, 44, 60). This antimicrobial treatment presumably occurred at, or after, the time of exposure.

Increasing antimicrobial resistance in foodborne pathogens may result in treatment failures, prolonged or more severe illness, increased hospitalisation, and increased mortality. As previously described, resistance is emerging to antimicrobial agents that are commonly used for the treatment of serious *Salmonella* infections; specifically fluoroquinolones in adults and extended-spectrum cephalosporins in patients of all ages. An example of probable treatment failures contributing to the death of patients was described by researchers in Denmark. Two patients with a multidrug-resistant *S.* Typhimurium DT104 infection died subsequent to treatment with fluoroquinolones. The infections were attributed to contaminated pork and traced back to a swine herd (55). Because *Salmonella* isolates from both the human and pork samples had decreased susceptibility to fluoroquinolones, treatment with that class of antimicrobials was determined to be a contributing factor in their deaths.

Increased severity of infection includes prolonged duration of illness, increased frequency of bloodstream infections, and increased hospitalisation. Studies have shown that fluoroquinolone-resistant *Campylobacter* infections result in a

median duration of diarrhoea that was several days longer than that of fluoroquinolone-susceptible infections (51, 64). Increased frequency of hospitalisation has also been associated with antimicrobial resistant *Salmonella* infections both in outbreak circumstances and in sporadic infections (32, 74). A study of sporadic *Salmonella* infections in 1989 and 1990 found that patients with resistant infections were likely to be hospitalised more frequently and for longer periods than patients with susceptible infections (39). Additionally, a greater case-fatality rate was associated with antimicrobial resistant *Salmonella* than with susceptible *Salmonella* in outbreaks from 1971 to 1983 (32). In Denmark, a study of culture-confirmed *S.* Typhimurium and *Campylobacter* infections from 1995 to 2000 showed an increased likelihood of bloodstream infection or death in the 90 days following specimen collection in persons with nalidixic acid, fluoroquinolone, or erythromycin resistant infections (84). Patients diagnosed with culture-confirmed *S.* Typhimurium infection in Denmark between 1995 and 1999 were followed for a period of two years and were found to have a higher two-year mortality rate than the general population. Those persons with naladixic-acid resistant and multidrug resistant infections had an even higher mortality rate than those with susceptible infections (30).

Conclusion

Because antimicrobial resistance is increasing among many bacterial strains, it has become an important public health challenge. Several different intervention strategies can be employed to prevent transmission of resistance from animals to humans. For example, Denmark and Sweden's decision to reduce the use of antimicrobial agents with human analogues as growth promoters was associated with reduced antimicrobial resistance and decreased public health risks (27, 65, 76, 84). In order to continue decreasing the number of pathogens becoming resistant, partners from the farming, veterinary, medical and public health communities will need to work together to prevent the misuse and overuse of antimicrobials.

A workshop on non-human antimicrobial usage and antimicrobial resistance was held by the WHO, the Food and Agriculture Organization of the United Nations and the World Organisation for Animal Health (OIE) in Geneva, Switzerland, in December 2003 (85). This collaborative effort recognised the need for action in both national and international arenas. Recommendations called for the implementation of the WHO global principles for the containment of antimicrobial resistance in animals intended for foods and OIE guidelines on responsible and prudent antimicrobial use (53, 83). Among the recommendations of these organisations are a call for enhanced surveillance of resistance and antimicrobial use, which is recognised as being essential for evaluating and directing prevention efforts.

In the USA, collaborative federal actions to address antimicrobial resistance in agriculture are outlined in the Public Health Action Plan to Combat Antimicrobial Resistance, released in 2001 by an interagency task force (35). Action items in this plan include improved surveillance of antimicrobial drug use and resistance, research and education, and, as a top priority item, refining and implementing FDA Guidance for Industry #152. This Guidance document proposes a modified approval process for antimicrobials used in animals (22). It intends to ensure the human safety of antimicrobials used in animals by prioritising these drugs according to their importance in human medicine. The American Veterinary Medical Association has promoted the education of veterinarians regarding the appropriate use of antimicrobial agents with published guidelines for their use (3).

The widespread use of antimicrobial agents in food animals is associated with increasing antimicrobial resistance in foodborne pathogens and subsequent multi-drug resistant bacterial infections in humans. Resistant pathogens are difficult if not impossible to treat and may result in severe illness or death. To address this public health problem, inappropriate use of antimicrobial agents in food animals and humans must be reduced. Guidelines for achieving this goal are already in place, but these guidelines must be well promoted among the veterinary and public health communities, because they will only be effective if they are stringently adhered to by professionals in both sectors.

L'antibiorésistance des agents pathogènes zoonotiques entériques

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Résumé
L'antibiorésistance constitue une menace sanitaire zoonotique. Comme en médecine humaine, l'utilisation d'agents antimicrobiens chez les animaux provoque l'apparition et la propagation de bactéries résistantes. Celles-ci peuvent se transmettre à l'homme par la chaîne alimentaire ou par contact direct, et entraîner des infections résistantes aux antibiotiques. La prévalence croissante de la résistance à certains agents antimicrobiens, comme les fluoroquinolones et les céphalosporines de troisième génération, a de sérieuses implications pour la santé publique, dans la mesure où ils jouent un rôle de premier plan dans le traitement des infections d'origine entérique. Les mesures destinées à contrôler la progression de cette résistance requièrent la collaboration de plusieurs partenaires, soit les éleveurs, les vétérinaires, les médecins et les autorités de santé publique.

Mots-clés
Agriculture – Animal producteur d'aliments – Antimicrobien – Campylobacter – Fluoroquinolone – Résistance – Salmonella – Transmis par les aliments.

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Resistencia a los antimicrobianos en patógenos intestinales zoonóticos

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Resumen
La resistencia a los antimicrobianos constituye una amenaza sanitaria zoonótica. En los animales, al igual que en el hombre, el uso de productos antimicrobianos conduce a la aparición y diseminación de bacterias resistentes. Éstas pueden transmitirse de los animales al ser humano por vías alimentaria o contacto directo y dar lugar a infecciones resistentes. La creciente prevalencia de patógenos resistentes a antimicrobianos como las fluoroquinolonas o las cefalosporinas de tercera generación, importantes para tratar infecciones causadas por patógenos intestinales, tiene notables repercusiones en materia de salud pública. Para impedir que esas resistencias sigan extendiéndose es necesaria la colaboración entre distintas profesiones: productores, veterinarios, médicos y especialistas en salud pública.

Palabras clave
Agricultura – Animal para consumo humano – Antimicrobiano – Campylobacter – Fluoroquinolona – Resistencia – Salmonella – Transmisión por vía alimentaria.

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